wherein said activation induces an increased delivery of said bioactive agent from said vasculature to said selected tissue.

165. (Amended) A method according to Claim 164 wherein said bioactive agent is administered to said patient by continuous intravascular infusion.

REMARKS

Reconsideration of the present application in view of the above amendments and following remarks is requested respectfully.

Status of Claims

Claims 116 to 184 are pending in the application. Claims 116, 117, 164 and 165 are amended herein. No claims have been added or canceled. Claims 132 to 137, 142 to 145, 152 to 159, 161 to 163, 167 and 175 to 177 have been withdrawn from consideration by the Examiner, as being directed to non-elected species.

The Amendments

The amendments to Claims 116 and 164 are made to clarify the steps and intended result of the methods of the present invention. The amended claims define methods for enhancing the delivery a bioactive agent to a selected tissue in a patient, that utilize ultrasonic energy-induced cavitation or rupture of a vesicle or acoustically active composition. The cavitation or rupture of the vesicles, in turn, causes an increased delivery of the bioactive agent from the vasculature into the selected tissue. The amendments are supported in the specification, for example, at page 5,

lines 14 to 17, where it is stated that the present invention is directed, *inter alia*, to methods for delivering bioactive agents to specific tissues and enhancing the uptake of those agents from the vasculature. Intravascular administration of the compositions is supported, for example, at page 71, lines 21 to 24. Applicant teaches the administration of the bioactive agent and/or the vesicle compositions so as to achieve a predetermined concentration of these elements within the vasculature of a selected tissue, for example at page 87, line 16 to page 90, line 21. Page 89, line 19, provides support for the use of the term "rupture."

Response to Rejections

Rejection under Section 112

Applicant respectfully submits that the amendments to the claims have rendered the objections under Section 112, second paragraph, moot. The term "enhancing the bioavailability" is no longer a part of the pending claim. The term "enhancing the delivery," which is included in amended Claims 116 and 164, is further clarified later in the claim, where it is stated that the application of ultrasonic energy in an amount sufficient to produce cavitation or rupture of the vesicle composition in turn "induces an increased delivery of said bioactive agent *from* the vasculature *to* said selected tissue." Thus, the term "enhanced delivery" would clearly be understood by one of skill in the art to refer to increased deposition of the bioactive agent within the selected tissue, as compared to the amount of bioactive agent that would generally be deposited absent the beneficial use of Applicant's methods.

The term "at a rate which comprises continuous infusion" is also no longer a part of these pending claims. In the methods defined by the amended claims, the compositions are administered "by continuous intravascular infusion."

In view of these amendments, Applicant respectfully requests that the rejections under Section 112 be withdrawn.

Rejection under Section 102

In the Office Action dated July 20, 2001, Claims 116 to 131, 138 to 141, 146 to 151, 160, 164 to 166, 168 to 174 and 178 to 184 stand rejected under 35 U.S.C. § 102(b) over Siegel et al, U.S. Patent 5,695,460 ("Siegel"). Applicant respectfully disagrees with the Examiner that these claims, in their previous form, were anticipated by Siegel. Applicant further respectfully submits that the amended claims clearly define over that reference.

Siegel is directed to methods for dissolving arterial thrombi (*i.e.* thrombi *within* the blood vessel). *See* col. 2, lines 2 to 5. The methods described by Siegel comprise injecting a patient with an echo contrast agent, either alone or in conjunction with a thrombolytic agent such as streptokinase, followed by the application of ultrasound. *See* col. 5, lines 17 to 28. As a result of the combined use of the echo contrast agent and ultrasound application, Siegel claims that one may produce "substantial dissolution of the thrombosis without the need for the introduction of thrombolytic agents" (*see* col. 5, lines 26 to 28 and 61 to 66), or one may "effect removal of the thrombosis in less time than required by the activity of the selected dose of thrombolytic agent without ultrasound radiation of the thrombosis." *See* col. 3, lines 11 to 13. Siegel further

proposes that the mechanism of action underlying the methods described therein may result from the increased cavitation of vascular fluid surrounding the thrombosis. (*See* col. 5, line 66 to col. 6, line 3).

In contrast to the methods described by Siegel, Applicant's claims define methods for delivering a bioactive agent to a selected tissue. As recited in amended Claims 116 and 164, this method comprises administration of ultrasound to increase delivery of the bioactive agent *out of the vasculature and into the selected tissue*. Siegel contains no teaching or suggestion of the use of ultrasound to accomplish such goals. Additionally, although Siegel may teach the administration of both a vesicle composition and a bioactive agent, followed by the application of ultrasound, Siegel cannot be said to inherently teach the method of the present invention because there is nothing in Siegel to indicate that the ultrasound energy is *necessarily* applied in an amount that would induce delivery of the bioactive agent from the vasculature into a selected, extravascular tissue, as recited in Applicant's claims. There is also nothing in Siegel to indicate that either the vesicle composition or the vasculature composition may be administered in such a fashion as to achieve a predetermined concentration of the bioactive agent and of a vesicle or accoustically active composition in the vasculature within a selected tissue, so that upon the application of ultrasound to that tissue, one may deliver a *calculated dose* of the bioactive agent to the selected tissue. The methods defined in the present claims, as amended herein, require such delivery. *See e.g.*, pages 87 to 90.

Siegel not only fails to teach or suggest the presently defined methods, it also completely fails to suggest the beneficial results that may be derived therefrom. For example, as also described in the specification, the methods of the present invention which target specific tissues for enhanced uptake of a bioactive agent potentially serve to lower the required dosage amounts, thereby minimizing toxic side effects and reducing costs to the patient. Similarly, increasing the deposition of a bioactive agent within a selected tissue may be used to deliver the agent to areas that suffer from poor capillary perfusion, providing delivery of the agent to tissues that might otherwise be inaccessible. *See e.g.*, page 4, line 19 to page 5 line 7. The Siegel patent contains absolutely no teaching or suggestion of such benefits, as Siegel is directed to other ends.

Since Siegel fails to teach all the elements of Applicant's claimed methods, and is in fact directed to entirely different ends, it is respectfully submitted that the claimed invention is clearly patentably distinct from anything described in Siegel. Accordingly Applicant respectfully requests that the rejection over Siegel be reconsidered and withdrawn.

Rejections under Section 103

Porter, the '098 Patent, and Schutt

Claims 116 to 131, 138 to 141, 146 to 151, 160, 164 to 166, 168 to 174 and 178 to 184 also stand rejected under 35 U.S.C. § 103 over Porter, et al., (Am Heart J. 1996 Nov; 132(5):964-968(Abstract)) ("Porter") in view of Porter, U.S. Patent No. 5,648,098 ("the '098 patent") and further in view of Schutt, et al., U.S. Patent No. 5,626,833 ("Schutt"). Applicant respectfully traverses this rejection.

As a preliminary matter, Applicant notes some apparent confusion in the wording of this rejection. In the Office Action, it is stated that the instant claims are directed to methods of lysing a thrombus. However, the claims that were pending at the time the Office Action was issued defined methods for "enhancing the bioavailability of a bioactive agent *in vivo*." It is noted that it was previously the position of the Patent Office that "methods for lysing a thrombus" and "methods for enhancing the bioavailability of a bioactive agent" define two distinct inventions. *See* Restriction Requirement dated April 11, 2000. Applicant is unclear as to whether the previously pending claims were misinterpreted, or whether it is the Examiner's position that the cited art, which is directed to lysing a thrombus, actually is covered by Applicant's methods for enhancing bioavailability.

In the event that the subject matter of the previously pending claims was not misinterpreted, Applicant respectfully submits that the amended claims, which are clearly directed to methods for delivering a bioactive agent, and more specifically, for improving delivery of the bioactive agent from the vasculature into a selected tissue, are neither taught nor suggested by Porter, either alone or in combination with the '098 patent and/or Schutt.

Much like Siegel, which was discussed above, Porter states that the combined administration of a microbubble contrast agent and a thrombolytic drug, followed by the application of ultrasound, provides improved clot lysis, compared with the use of either the thrombolytic or ultrasound alone. There is simply nothing in Porter to suggest the methods of

the present invention, which are directed to increasing delivery of a bioactive agent out of the vasculature and into a selected tissue.

The deficiencies of Porter are not remedied by the combination of that reference with either the '098 patent or Schutt. Like Porter, the '098 patent is directed to methods for lysing a thrombus. *See* Abstract. As such, the '098 patent contains absolutely no teaching or suggestion that ultrasound can be utilized to improve the delivery of a bioactive agent to a selected tissue. Thus, the '098 patent adds nothing that makes up for the deficiencies of Porter

Moreover, the '098 patent teaches the use of a microbubble contrast agent, followed by the application of ultrasound *without* the use of a thrombolytic agent. *See* col. 3, lines 6 to 8. In fact, it is stated in the '098 patent that thrombolytic agents have many drawbacks, and it is an object of that patent to provide a thrombolytic therapy that avoids the use of such drugs. *See* col. 2, lines 13 to 16. Thus, the '098 patent *teaches away* from the methods of the present invention, which are specifically directed to the *combined* use of a vesicle or accoustically active composition and a bioactive agent.

Schutt is of equally little use in overcoming the deficiencies of Porter and the '098 patent. Schutt, in fact, is directed to ultrasound *imaging*, not drug delivery, and it contains nothing to suggest that ultrasound can be used in accordance with the methods of the present invention.[1]

[1]Applicant notes that it states at col. 11, lines 25 of Schutt that the microbubble preparations described therein can be used to enhance visualization of changes in myocardial tissue due to various interventions, such as the use of thrombolytic agents. Applicant respectfully submits that this passage completely fails to teach or suggest the methods of improved delivery defined by the present claims.

Aside from the fact that this reference may teach the use of certain gases and vesicle compositions, it completely fails, even in combination with Porter and/or the '098 patent, to teach or suggest the methods of the present invention.

Since Porter, the '098 patent and Schutt, either alone or in any proper combination, fail to teach or suggest the invention defined by Applicant's claims, it is respectfully requested that the rejection under Section 103 over these references be withdrawn.

Siegel

Claims 141 and 146 to 151 also stand rejected under Section 103 over Siegel. Applicant again expresses confusion regarding this rejection. As stated above, Siegel is directed to lysis of a thrombus, and in the Office Action, Applicant's claims are treated as if they were directed to the same ends. However Applicant's claims, both as previously pending and as amended herein, are directed to methods for *delivering a bioactive agent*, and more specifically, for improving the delivery of a bioactive agent out of the vasculature and into a selected tissue. Siegel is simply directed to a different purpose, and that reference fails to teach or suggest either the recited claim steps or the beneficial results that flow therefrom. Accordingly, Applicant respectfully requests that the rejection be withdrawn.

Porter in view of Siegel

Claims 116 to 131, 138 to 141, 146 to 151, 160, 164 to 166, 168 to 174 and 178 to 184 also stand rejected under Section 103 over Porter in view of Siegel.

It is stated in the Office Action that this combination is made because Porter and Siegel are in the same field of endeavor, *i.e.*, the enhancement of thrombolytic activity. Applicant respectfully submits that though this may well be the case, neither of these references are directed to the delivery of a bioactive agent, specifically the improved delivery of a bioactive agent out of the vasculature and into a selected tissue, as is the subject of the present claims. As discussed at length above, there is simply nothing in either of these references to teach or suggest the methods presently claimed. Accordingly, Applicant respectfully requests that the rejection be withdrawn.

Double Patenting Rejections

Claims 116 to 131, 138 to 141, 146 to 151, 160, 164 to 166, 168 to 174 and 178 to 184 stand rejected under the judicially created doctrine of obviousness-type double patenting over U.S. Patent Nos. 6,143,276, 6,1232,923, 5,770,222, and 5,580,575. Applicants respectfully request that these rejections be reconsidered in light of the claim amendments submitted herein. Should any of these rejections be maintained, Applicant intends to file a terminal disclaimer as provided in 37 C.F.R. § 1.130(b) once the Examiner has issued a favorable ruling indicating that the amended claims will be allowed. Applicant will be filing the terminal disclaimer to facilitate prosecution and Applicant expresses no opinion as to whether the obviousness-type double patenting rejection is warranted in view of the aforementioned patents.

Claims 116 to 131, 138 to 141, 146 to 151, 160, 164 to 166, 168 to 174 and 178 to 184 also stand provisionally rejected under the judicially created doctrine of obviousness-type double

patenting over the pending claims of copending Application Serial No. 09/218,660 ("the '660 application"). Applicants respectfully request that this rejection also be reconsidered in light of the claim amendments submitted herein. Should the rejection over the '660 application be maintained, Applicant reserves the right to address such rejection once a claim is allowed in that application.

Cancellation of Non-Elected Species

It is stated in the Office Action dated July 20, 2001 that since the election was made without traverse, Applicant is required to cancel the claims directed to non-elected species. Applicant respectfully disagrees.

First, Applicant notes that the withdrawn claims are directed to non-elected *species*, not to a separate invention, as stated in the Office Action. Second, attention is directed to M.P.E.P. § 809.02(c)(B), where it is stated that if a generic claim is subsequently found to be allowable, and not more than a reasonable number of additional species are claimed, where all claims to each of the additional species are embraced by an allowable generic claim, applicant must be advised of the allowable generic claim and that claims drawn to the non-elected species are no longer withdrawn. Applicant further notes that the statement in M.P.E.P § 821.01, referred to in the Office Action, regarding cancellation of claims to non-elected species, is for use in *final* rejections. The instant Office Action is not final.

Accordingly, it is Applicant's understanding that if and when a generic claim encompassing all of the non-elected species claims is determined to be allowable, the search will be expanded to cover the entire scope of Applicant's generic claim.

CONCLUSION

Applicant believes that the foregoing constitutes a complete and full response to the Office Action of record. Applicant earnestly requests reconsideration of the application and withdrawal of the pending rejections. Upon a determination that the generic claims are allowable, Applicant respectfully requests that the withdrawn claims be examined.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Respectfully submitted,

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Version With Markings To Show Changes Made

Claims 116, 117, 164 and 165 have been amended, as follows:

116. (Amended) A method for enhancing the [bioavailability] delivery of a bioactive agent [*in vivo*] to a selected tissue in a patient, said method comprising:

(i) administering said bioactive agent to [a] said patient, by a route of administration sufficient to achieve a predetermined concentration of said bioactive agent within the vasculature of said selected tissue;

(ii) administering a vesicle composition to said patient, by continuous intravascular infusion for a time sufficient to achieve a predetermined concentration of said vesicle composition within the vasculature of said selected tissue, wherein said vesicle comprises [comprising], in an aqueous carrier, [a gas or gaseous precursor and] vesicles comprising lipids, proteins or polymers and a gas or gaseous precursor [to the patient,]; and

(iii) applying ultrasonic energy to [the patient] said selected tissue in an amount sufficient to produce cavitation or rupture of said vesicles,

wherein [said vesicle composition is administered to said patient at a rate which comprises continuous infusion] said cavitation or rupture of said vesicles induces an increased delivery of said bioactive agent from said vasculature to said selected tissue.

117. (Amended) A method according to Claim 116 wherein said bioactive agent is administered to said patient [at a rate which comprises] by continuous intravascular infusion.

164. (Amended) A method of enhancing the delivery of a bioactive agent [in] to a selected tissue [*in vivo*] in a patient, said method comprising:

(i) administering said bioactive agent to [a] said patient, by a route of administration sufficient to achieve a predetermined concentration of said bioactive agent within the vasculature of said selected tissue;

(ii) administering an acoustically active composition to said patient, by continuous intravascular infusion for a time sufficient to achieve a predetermined concentration of said acoustically active composition within the vasculature of said selected tissue; and

(iii) applying ultrasonic energy to said selected tissue in an amount sufficient to activate said acoustically active composition,

wherein [said acoustically active composition is administered to said patient at a rate which comprises continuous infusion] the activation induces an increased delivery of said bioactive agent from said vasculature to said selected tissue.

165. A method according to Claim 164 wherein said bioactive agent is administered to said patient [at a rate which comprises] by continuous intravascular infusion.